Review Article

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Correlation between Sex Hormone Deficiency and Osteoarthritis

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Abstract

This literature review explores recent and past investigations carried out by researchers in various settings pertaining to the orthopaedic field of medicine, in attempts to show a possible connection between the deficit in sex hormone levels and the potential consequences it brings about on orthopaedic health, namely, osteoarthritis. There is some evidence in the literature suggesting that suboptimal concentrations of steroid hormones can negatively impact bone health, making it more susceptible to physical injury, especially when the hormone in question is estrogen. Several studies have shown that this biomolecule is quite essential to human health due to its effects on not only sexual development and function but also on bone metabolism, in both men and women. Investigations revolving around estrogenic compounds reveal their significance in physical capacitation of adult individuals, since it has already been found that estrogens play a pivotal role on bone maintenance by directly interacting with osteocytes, osteoblasts, osteoclasts and even T-cells, to name a few examples. Large scale studies also bring up plausible evidence by evaluating the links between measured sex steroid concentrations and incidence of osteoarthritic joint replacement in adults. Taking that into consideration, there is sufficient motivation to look into hormonal fluctuation in adult individuals, calling for suitable medical intervention in order to keep a patient's health under control, avoiding and even treating the detrimental effects caused by the deficiency of certain steroid hormones.

Keywords: Osteoarthritis, Estrogen, Testosterone, Bone metabolism, Menopause

Introduction

Osteoarthritis (OA) is a major degenerative joint disease which can affect more than one quarter of the global population in individuals over the age of 18. This disease is typically defined by the following observations: progressive loss of articular cartilage, thickening of the subchondral bone, and formation of osteophyte, significant inflammation of the synovial as well as degeneration of ligaments and menisci of the knee and hypertrophy of the

joint capsule. Risk factors for OA encompass joint injury, obesity, aging and even genetic predisposition [1-3]. The pathological changes involved in the progression of OA are caused by biomechanical forces as well as multiple autocrine, paracrine and endocrine cellular events which all contribute to perturbations of tissue homeostasis within the affected joint [4],[5]. Gonadal steroid hormones, such as Estrogen (E) and Testosterone (T), for example, are molecules that are biosynthesized in the body and play a key role in sexual development and reproduction, which

includes regulating the vital process of skeletal growth and maturation, among other natural developmental processes in both men and women [6]. Sex hormones control the development of cartilage and bone as well as homeostasis according to sex. There are recent in vitro studies suggesting that 1 α ,25-dihydroxyvitamin D3 [1 α ,25(OH) $_2$ D $_3$], the vitamin D3 metabolite, also has sex-specific effects on musculoskeletal cells, therefore indicating that vitamin D3 metabolites may elicit an effect on sex-specific differences related to osteoarthritis [2]. Other studies show that estrogen is the key regulator of bone metabolism in both male and female individuals. This hormone has direct effects on osteocytes, osteoblasts and osteoclasts and also inhibits activation of osteoclasts either directly or by cooperation with osteoblasts and T-cells. As figure 1 illustrates, the central role of estrogen on the skeletal system is to avoid the resorption of bone while promoting its formation [7]. This alludes to the belief that a decrease in levels of sex hormones may be positively correlated to bone disorders and orthopaedic complications. In these articles, the authors will explore basic science and the role of sex steroid hormones in musculoskeletal health and possible correlations between their levels and incidence of disorders of the locomotor apparatus, such as osteoarthritis.

Sex hormones: a physiological perspective

Androgen biosynthesis

Firstly, gonadotropin-releasing hormone, produced by the hypothalamus, stimulates the synthesis and secretion of luteinizing hormone and follicle stimulating hormone in the anterior pituitary gland, where luteinizing hormone enters the circulation and reaches the gonads, finally activating the synthesis and secretion of testosterone. In comparison with women, men hold about 95% of their androgen production in the Leydig cells of the testicles and have around 20 to 25 times more testosterone. Testosterone elicits its effects in the body upon binding to the intracellular androgen receptor, thereby translocating to the nucleus where the receptor-ligand complex triggers gene transcription. When properly secreted and circulating in sufficient levels, this sex hormone is responsible for several physiological effects such as increase in bone density, muscle mass, libido, development of secondary sexual characteristics and more [8-11].

Estrogen biosynthesis

Estrogen is the primary female sex hormone secreted mainly by the ovaries and placenta but is also generated by the peripheral steroidogenic conversion by the testicles

in men, albeit to a lesser a degree. Additionally, this hormone is found in greater amounts in women, about 4 times the amount compared to men. Estrogen promotes the development of female sexual characteristics and inhibits the secretion of follicle-stimulating hormone by the pituitary gland via a negative feedback mechanism. Its actions are mediated by the Estrogen Receptors (ERs), which are synthesized in many cell types in either of the two forms: ER α or ER β , which function as transcription factors provided that ligand-binding occurs [12]. ER α is expressed in several tissues, such as bone, white adipose tissue, and muscle, to name a few, whereas ER β is notably expressed in colon, prostate, testicles, salivary gland, bone marrow, and vascular endothelium. Primarily, estrogens play a key role in developing and maintaining regular sexual and reproductive function in women. In addition, it has also been observed that this hormone can exert a broader range of biological functions in both men and women, for example the attenuation of post-injury disruption and inflammatory responses, protection against oxidative stress and muscle damage. Furthermore, Estradiol (E $_2$), a natural estrogenic hormone, has been shown to affect satellite cell activation and proliferation, enhancing cellular growth and recovery; myosin function, however, is affected by age and Estradiol levels, in women [8],[13].

A microscopic view on bone adaptation

Bone is a complex tissue capable of adapting to daily biomechanical forces distributed across the limbs via a process known as mechanotransduction. This process is regulated by mechanosensitive osteocytes, cells which have the ability to receive mechanical signals and transduce them into chemical responses such as the release of signalling molecules that initiate the recruitment and management process of osteoblasts, the bone-forming cellular agents; or osteoclasts, the cellular units responsible for bone resorption [14-16]. It has been found that the production of mechanically-efficient bone architecture is dependent on the biomechanical signal intensity and spatial distribution as well as the response generated by the osteocytes. It is known that estrogen plays a pivotal role in bone maintenance and can directly interact with osteocytes, and, additionally, it has also been discovered that estrogen deficiency alone interferes with the anabolic effect of mechanical stress [15]. Some studies even show that this hormone stimulates proteoglycan changes in cartilage, either directly or indirectly through cytokines and, identification of estrogen receptors ER α and ER β on human articular chondrocytes confirm that cartilage is sensitive to estrogen [17]. Scarcity of this steroid hormone leads to increased osteoclast recruitment and, therefore, enhanced

bone resorption as well as impaired mechanosensitivity and mechanotransduction, compromising the optimal level of osteoblast activity in bone deposition. In other words, the combination of impaired mechanosensitivity and estrogen deficiency might culminate in structural weakness and bone fragility. These findings would then suggest that estrogen-deficient patients may very well experience a reduced effectiveness of mechanic stimulus overall as osteoblast activity would then become limited.

Figure 1: The involvement of estrogen in bone turnover via effects on osteocytes, osteoblasts, osteoclasts and T-cells [7].

Biomechanics and bone health

It is well known that bone tissue adapts its mass and structure in response to mechanical loading, according to German anatomist and surgeon Julius Wolff, responsible for conveying the term “Wolff’s Law” in the 19th century. The medical community also shows that physical inactivity can result in osteopenia, a condition characterized by reduced bones mass; however, mechanical stimulus can regulate and prevent the harmful consequences of disuse [15]. Another highly relevant principle which relates to the aforementioned concept is the widely popular hypothesis established by medical experts that illustrates the mechanosensitive properties of osteocytes, the “mechanostat” theory, first introduced by Harold Frost in 1987. Frost proposed that bone operates via a homeostatic regulatory mechanism with a certain threshold, above or below a set point where either bone formation or resorption occurs. Following that line of thought, it has also been theorized that in conditions such as postmenopausal osteoporosis, the threshold value that dictates bone formation or resorption might suffer an alteration, which would therefore complicate the standard process of mechanical loading involved in maintaining bone mass [14,15,16].

The importance of aromatase in hormonal regulation

Androstenedione (ASD) is a vital precursor for the biosynthesis of Testosterone (T), Estradiol (E2) and Androstenediol glucuronide (Ag) in non-gonadal tissues. When it comes to estrogen and its involvement in bone metabolism, the aromatase enzyme plays an important function in converting Androstenedione to estrone in human bone cells, contributing to the maintenance of long-bone growth. In men, for example, testosterone is secreted by the testicles but is also produced from Dehydroepiandrosterone (DHEA). In circulation, DHEA is converted to testosterone by Ag and Androstenedione. Testosterone and Androstenedione are then converted to E2. In animals, research suggests that Androstenedione has been linked to increasing bone mineral density (BMD) at metaphyseal and diaphyseal femoral regions as well as bone mineral quality and quantity of cancellous and cortical bone. The findings, however, do not clarify whether or not such effects come from a direct action of Androstenedione itself or the involvement of aromatase in the conversion of the steroid precursor to T, E2 or Ag within bone tissue [9],[13],[18].

There are also other examples of the involvement of aromatase in bone metabolism. The correlation between Estradiol and bone remodelling biomarkers has been proposed by a study where elderly men treated with an aromatase inhibitor displayed a significant increase in bone resorption as well as decreased bone formation biomarkers; once again suggesting that aromatase in combination with steroid precursors is relevant to bone health, especially in aged individuals [6].

Aging patient

The more the patient ages the more their sex steroid levels decline, especially in bioavailable fractions for both testosterone and Estradiol, in both sexes. Andropausal men suffer reduced levels of testosterone, a condition that is usually responsible for a decrease in muscle mass, bone mass and physical function. It was long thought that testosterone alone was considered to be the most crucial factor related to bone loss and fracture in males; however, recent findings have revealed that Estradiol levels are even more related to the bone loss and fracture in men [19]. In menopausal women, the drop in levels of sex hormones, especially Estradiol, and consequential effects on bone, has been well documented but it is not completely clear whether or not loss of this hormone negatively impacts muscle mass and physical function [3],[8]. Females

suffer a great decrease in Bone Mineral Density (BMD) during menopause and seem to be at a greater risk of bone loss at the Lumbar Spine (LS) in comparison to the hip regarding risk fractures. Women with lower levels of free Estradiol but higher proportions of Sex Hormone Binding Globulin (SHBG) face increased risk of fracture, although there seems to be no correlation between circulating testosterone levels and fractures. On the other hand, hypogonadal men with low BMD experience more fractures even though the association between circulating testosterone and skeletal health is not entirely consistent. However, low bioavailability of estrogen and high SHBG concentrations in men are seemingly associated with more fracture incidents and increased bone loss (Cauley, 2015). This suggests that the level of testosterone alone is not the only limiting factor involved in the musculoskeletal health of elderly patients. Instead, it may very well be the case where Estradiol might actually be more relevant in these scenarios given the fact that it is known to play a key role in muscle strength. Studies on mice, for example, show that low levels of Estradiol are associated with the low force-generating capacity of posterior limbs even with controls for physical and muscular activities. Conversely, when Estradiol replacement occurs, decrease in strength is fully recovered, an observation which therefore implies the importance of this hormone on contractile function of muscle [8].

Sex steroid hormone concentrations and musculoskeletal health

A prospective cohort study published in 2014 by Hussain et al [20] exploring the correlation between concentrations of circulating sex steroid hormones and the likelihood of total knee and hip replacement for OA in women revealed that low Estradiol levels pose a risk factor for knee OA, whereas low Androstenedione concentrations and high sex hormone binding globulin (SHBG) levels contribute to the development of hip OA. To clarify these observations, Hussain and colleagues reported that women who underwent total knee replacement had a greater Body Mass Index (BMI) than those with no history of joint replacement. Also, it was seen that in women with total joint replacement there was a lower median serum concentration of ASD, Estrone sulphate and Estradiol in comparison with the ones who did not undergo such procedure. Lastly, the observations for women who had undergone total hip replacement revealed a higher median concentration of SHBG relative to other groups. Regarding statistical analyses, the authors concluded via univariate analyses that the log-transformed concentration of E2 was inversely associated with the incidence of total knee

replacement, and the log-transformed concentration of ASD was inversely associated with the incidence of total hip replacement. Conversely, the log-transformed concentration of SHBG was positively associated with the incidence of total hip replacement. Furthermore, a similar study published in 2016 by Kruij et al [21] proposes that lower sex hormone levels are also associated with an increased risk for having and developing chronic musculoskeletal pain, in a manner that is not dependent on lifestyle and health-related factors, in women. In their investigation, De Kruij and colleagues concluded that lower levels of Androstenedione, testosterone, and Estradiol resulted in higher risk for chronic hand pain, in particular. These observations suggest that circulating sex steroids may influence the pathogenesis of orthopedic diseases, namely, osteoarthritis. Therefore, if the concentrations of these hormones are controlled by methods such as Hormone Replacement Therapy (HRT), it may be possible to effectively prevent and treat knee and hip OA, for instance. The next section of this paper will explore the possible alterations in articular tissues as a result of estrogen deficiency.

Estrogen deficiency and articular cartilage alterations

It is now known that articular tissues respond to estrogens due to the presence of ERs, demonstrated in cartilage, bone, synovial, ligaments and muscle [8],[13]. Additionally, estrogens influence the metabolism of articular tissues via many complex molecular mechanisms on many levels. Important cellular events in joint tissues are regulated by estrogens, which can be seen by differential bone alterations in ER knock-out mice [22]; decreased nitric oxide production when interaction between ER and $\text{nf-}\kappa\beta$ (nuclear factor-kappa beta) in chondrocytes [23]; increase in proteoglycan biosynthesis by chondrocytes and anti-apoptotic events in bone and skeletal muscle cells via phosphatidylinositol-3-kinase/Akt and mitogen activated protein kinase pathways [24]; the bone's ability to sustain mechanical forces due to the nuclear interaction of ERs with components derived from the Wnt signaling pathway [25]. Furthermore, there is also the inhibition of osteoclast activity in bone resorption by osteocytes as a result of TGF- β (transforming growth factor-beta) activity enhancement modulated by estrogen [26], and the up-regulation of a functional uridinediphosphate-glucose dehydrogenase in articular chondrocytes [27]. These beneficial cellular effects can be lost due to postmenopausal ovarian insufficiency, for example. The effects of estrogen depend on the amount administered, which are not always beneficial, particularly when given in high concentrations, with the risk of serious

adverse effects in cartilage and joint ligaments [5].

There is a correlation between estrogen deficiency and OA changes in articular tissues. In mature female animals, drops in estrogen levels after a surgically induced ovarian insufficiency may be detrimental to cartilage homeostasis and subchondral bone turnover during OA development and progression [28]. In previous studies, increase in cartilage turnover and development of erosions on the surface of articular cartilage were observed in OA ovariectomized Sprague–Dawley rats, guinea pigs and cynomolgus macaques subjected to bilateral ovariectomy [29],[30]. Researchers found that the indices of bone turnover were higher in subchondral bone in comparison to epiphyseal/metaphyseal cancellous bone of the proximal tibia in ovariectomized cynomolgus monkeys. Bone volume and trabecular number and thickness were also considerably higher in osteophyte bone than in tibia epiphyseal/metaphyseal cancellous bone [31],[32]. Another study on a rabbit model, conducted by Herrero-Beaumont and colleagues in 2008 [5], revealed that ovariectomy-induced estrogen deficiency leads to mild OA changes in healthy articular cartilage, whereas ovariectomy and glucocorticoid-induced osteoporosis contribute to the development of osteoarthritic changes. The authors reported that ovariectomy only caused mild bone mass loss and moderate doses of glucocorticoids ensured the development of osteoporosis. Therefore, the effects of estrogen deficiency could have a direct action on articular cartilage and an indirect effect on subchondral bone. Low BMD of subchondral bone may intensify pre-existing cartilage damage. In other words, it was observed that osteoporosis was followed by surgically induced OA in rabbits, indicating that osteoporosis aggravated OA progression and severity. They also proposed that estrogen deficiency after ovariectomy may affect repair of post damaged skeletal muscle, accompanied by increase in fat mass, with a subsequent increase in synthesis of adipokines, particularly leptin, which promotes cartilage degradation.

Conclusion

To summarize all the material hereby presented in this literature review, it can be seen that with all the previous observations made by researchers, there seems to be a link between insufficient levels of sex steroid hormones and musculoskeletal disorders. While there is refined evidence reinforcing the biological effects of hormones on health, most of the investigations are more seemingly inclined towards female biology of both human and animal models, especially in postmenopausal women where the

drop in estrogen levels generate more pronounced effects. It is quite evident that estrogen and testosterone, the two main steroidogenic compounds in the human body, are both equally important in the physical development and maintenance of a healthy musculoskeletal system, however, it is now more apparent that estrogen is much more than just a primary female sex hormone involved in sexual development. In this review, much attention has been given to estrogen, especially because of the reported direct interactions with important microscopic units, such as osteoblasts, osteocytes and osteoclasts, cells which dictate bone formation or resorption. In addition, it must also be reiterated that estrogens have been evaluated in animal studies to show relevance on force generating capacity of locomotor structures, once again suggesting how this biomolecule is vital for the maintenance of structural stability. The enzymatic activity of aromatase in the conversion of androgens to estrogens, particularly, testosterone to Estradiol, is another important observation that must not be obliterated. It also serves the purpose to show that testosterone has significance in this process after much appraisal of estrogen. To finalize, it is evident that numerous studies suggest that circulating sex steroids influence the pathogenesis of musculoskeletal disorders, such as osteoarthritis. A suitable approach to rectify such a medical condition would be to modify the concentrations of hormones in a supplemental manner via methods such as Hormone Replacement Therapy (HRT), providing the possibility to effectively modulate and prevent osteoarthritis of coxal and patellofemoral joints, for instance.

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